

Effect of longterm misoprostol coadministration with non-steroidal anti-inflammatory drugs: a histological study

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Abstract

Prostaglandins are widely used in the prevention and healing of non-steroidal anti-inflammatory drug (NSAID) induced gastric and duodenal ulcers, but their longterm effect on the human gastric mucosa is unknown. This study assessed the effect of coadministration of prostaglandins with NSAIDs on the histology of the gastroduodenal mucosa. Histological appearances (using the Sydney system) of gastric biopsy specimens from 180 patients receiving longterm NSAID treatment of whom 90 had been receiving misoprostol (400–800 µg/day) for one to two years were studied. Both groups of patients were comparable with regard to clinical and demographic details. There was no significant difference ($p>0.1$) in the prevalence of chronic gastritis (total, corpus or antrum only) between patients receiving (36 of 90 (40%)) or not receiving misoprostol (35 of 90 (39%)). Chronic gastritis was equally associated with the presence of *Helicobacter pylori*, 86% and 73% ($p>0.1$), respectively, in the two groups. Significantly fewer patients receiving misoprostol had reactive gastritis than those receiving only NSAIDs (8 (9%) versus 27 (30%), $p<0.01$). Reactive gastritis was not associated with *H. pylori*. Thirty nine (43%) of the misoprostol treated patients had normal histology compared with 16 (18%) receiving only NSAIDs ($p<0.01$). These results show two different patterns of gastric damage in patients receiving NSAIDs, namely chronic and reactive gastritis. Misoprostol treatment was associated with a significantly reduced prevalence of reactive gastritis and it is suggested that this, along with its antisecretory action, may explain the reduced prevalence of gastroduodenal lesions when coadministered with NSAIDs.

(Gut 1995; 37: 195–198)

Keywords: NSAID, reactive gastritis, misoprostol, NSAID gastropathy.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed of the anti-rheumatic drugs, which attests to their efficacy in reducing joint pain and inflammation. The main concern about their use is the frequency of gastrointestinal damage and its attendant complications.^{1,2} Point

prevalence studies show that 10–25% of patients receiving NSAIDs have gastric or duodenal ulcers, which have the propensity to perforate or bleed.^{3–6} It is estimated that the serious complications of NSAIDs on the gastroduodenal mucosa may lead to 15–30 000 hospital admissions, which account for up to 4000 premature deaths in the United Kingdom annually.^{6–8} Sixty to 70% of patients receiving NSAIDs develop small intestinal inflammation, which may be associated with blood and protein loss contributing to iron deficiency and hypochromic anaemia.²

Because of the high prevalence of gastric and duodenal ulcers in patients receiving NSAIDs and the seriousness of the possible complications, a major effort has been made to establish the efficacy of various drugs in the healing of established lesions and their possible prevention. Collectively the data to date suggest that prostaglandins, H_2 receptor antagonists, and proton pump inhibitors are all of comparable efficacy in healing of NSAID associated gastric and duodenal ulcers and in preventing duodenal ulcers when given concomitantly with NSAIDs.⁹ The different classes of drugs differ, however, in their efficacy to prevent the development of gastric ulcers; prostaglandins being the only agents of confirmed efficacy in double blind, placebo controlled, and comparative trials.^{9,10}

An increasing number of patients receiving NSAIDs are likely to be co-treated, with the prostaglandin analogue misoprostol longterm in the hope that this will reduce the frequency of NSAID associated ulcers and their serious complications (bleeding and perforation). The longterm safety of such treatment is evident clinically, but no study has looked at the possible adverse effect of misoprostol on the histology of the gastric mucosa when given longterm with NSAIDs. This could be important in view of the fact that prostaglandins play an important part in the regulation of cell proliferation.^{11,12} Besides direct effects on cell proliferation visible on light microscopy such as epithelial cell hyperplasia and even dysplasia the protective effect of prostaglandin analogues may be reflected in a reduced susceptibility of the gastric mucosa to *Helicobacter pylori* associated chronic gastritis or reactive gastritis (chemical gastritis, type C gastritis). We therefore compared the histological appearances of gastric biopsy specimens from patients receiving longterm NSAID treatment without misoprostol with those from patients receiving NSAIDs and concomitant misoprostol for periods of either one or two years.

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Accepted for publication
25 November 1994

TABLE I Inclusion and exclusion criteria for the two study populations

Inclusion criteria	Exclusion criteria
Male or female >18 years	Women of childbearing age
Diagnosis of arthritis requiring NSAIDs	Patients with the following conditions
Rheumatoid arthritis	Inflammatory bowel disease
Ankylosing spondylitis	Malignancy of any type
Osteoarthritis	Gastrinoma/Zollinger-Ellison syndrome
Psoriatic arthritis	Significant renal or hepatic disease
	Alcoholism
	Hypersensitivity to misoprostol
	Previous gastric or duodenal surgery
	Patients requiring
	Antiulcer drugs
	Anticoagulants
	Corticosteroids

Methods

There were two sources of histological material. Firstly, biopsy specimens obtained from 90 patients receiving longterm NSAID treatment attending rheumatology outpatients at Northwick Park Hospital. Most of these (n=58) had previously participated in a detailed investigation of the prevalence and severity of NSAID enteropathy, its possible complications, and treatment.¹³ The remaining 32 had participated in a similar study directed to investigate the site of intestinal bleeding in patients receiving NSAIDs.¹⁴ All of these had undergone endoscopy with biopsy from standard sites (duodenum, antrum, and body) as a part of these investigation.

Secondly, there was histological material from 90 patients receiving longterm NSAID treatment who had been concomitantly receiving misoprostol (400–800 µg/day) for one or two years. These patients had initially been recruited in a multicentre study assessing the short term (two weeks) effect of prostaglandins in the prevention and healing of NSAID induced gastroduodenal lesions.¹⁵ The 90 patients reported on here continued taking misoprostol with their NSAID in the long term. The study at Northwick Park Hospital and the multicentre study both had common entry and exclusion criteria (Table I).

Histological assessment

All patients underwent endoscopy under sedation. Two biopsy specimens were taken from each of three sites; the duodenal bulb, the greater curve of the antrum at least 2 cm from the pylorus, and the mid greater curve of the body. In a case with ulceration close to the landmarks the samples were taken 2 cm from the crater. All samples were treated in an identical fashion, routinely formalin fixed, and paraffin processed. Sections (3 µm) were cut and stained with haematoxylin and eosin. A Cresyl fast violet stain was used to facilitate the identification of *H pylori* like organisms.

For the purposes of this study only the antral and body biopsy specimens are reported in detail. Gastritis was assessed according to the Sydney system.¹⁶ The slides from all 180 patients were collected at one centre (NPH) and labelled with coded numbers unknown to

the examining pathologists. This was to limit any observer bias created by knowledge of the origin of the slides. At the end of the study the slides were decoded. Interpretation was carried out independently by two pathologists and there was good observer agreement in classifying the biopsy specimens appearances. In cases of disagreement this was resolved by the third histopathologist.

Statistics

Statistical differences between demographic data were assessed with the Wilcoxon's rank sum test and histopathological data by the χ^2 test.

Results

Patients

There were no significant differences in demographic details of patients in the two groups. In particular there was no significant difference between the male to female ratio, mean (SD) age (62 (12) v 59 (8) years, respectively), age range or number of patients in each age group (20–40, 41–60, and over 61 years old), number of patients with osteoarthritis, rheumatoid arthritis or other arthritides, type of NSAID received, prevalence of gastroduodenal ulcers before this study or duration of NSAID treatment.

Histological assessment (Table II)

The abnormal histological categories identified were chronic gastritis, reactive gastritis, and mixed patterns of the two. Thirty five patients receiving NSAIDs only had chronic gastritis compared with 36 receiving NSAIDs and misoprostol ($p>0.1$) (Fig 1). Most of these were associated with the presence of *H pylori* (28 of 35 (73%) receiving NSAIDs alone and 31 of 36 (86%) receiving NSAIDs and misoprostol, $p>0.1$). There were no significant ($p>0.1$) differences between the two groups in the graded histological parameters (severity of inflammation, etc), as defined by the Sydney system. Seven patients receiving NSAIDs alone and four patients receiving NSAIDs and misoprostol had minimal inflammatory changes considered to be just outside the limits of normality.

Reactive gastritis was seen in a total of 35 patients (Fig 2) and in all cases these were

TABLE II Histopathological details of gastric biopsy specimens obtained from patients receiving NSAIDs with and without coadministration of misoprostol

Histological findings	NSAIDs	NSAIDs with misoprostol
Chronic pangastritis	23 (20)	23 (21)
Chronic gastritis of corpus	5 (2)	2 (1)
Chronic gastritis of antrum	7 (6)	11 (9)
Minimal inflammatory change	7 (0)	4 (0)
Reactive gastritis (reflux, type C)	27 (0)	8 (0)*
Mixed group	5 (0)	3 (0)
Normal	16 (0)	39 (0)*

The Table shows the number of patients in each group (n=90) with specific histological findings in gastric biopsy specimens. The number positive for *H pylori* is shown in parenthesis.

*Differed significantly between the two groups, $p<0.01$.

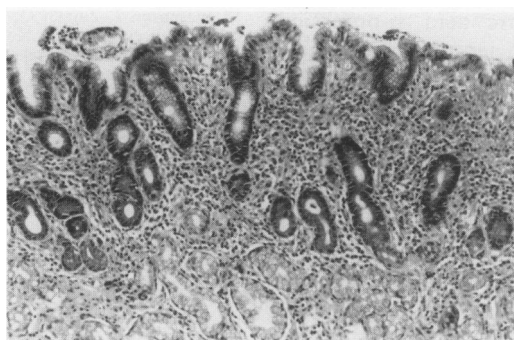


Figure 1: Typical *H pylori* associated chronic antral gastritis. There is moderate chronic inflammation in the superficial half of the mucosa, an intact surface, and minimal or no activity in the form of neutrophil infiltration (haematoxylin and eosin, original magnification $\times 160$).

changes confined to the gastric antrum. Patients receiving NSAIDs alone had a significantly ($p < 0.01$) greater prevalence of reactive gastritis than those receiving concomitant misoprostol (27 (30%) versus 8 (9%), respectively) and in no case was reactive gastritis associated with the presence of *H pylori*. Eight patients had a mixed picture of chronic and reactive gastritis and none of these was associated with *H pylori*.

Sixteen patients (18%) receiving NSAIDs had a normal histological examination, which was significantly less ($p < 0.01$) than that found in patients receiving concomitant misoprostol (39 (43%).

No biopsy sample showed any signs of dysplasia or neuroendocrine cell hyperplasia.

Discussion

This study has shown that longterm misoprostol ingestion together with NSAIDs is not associated with any new pattern of gastric pathology nor any worrying hyperplastic or dysplastic changes. The last factor was a theoretical possibility because of the importance of prostaglandins in the regulation of cell proliferation.^{11 12}

Our studies confirm much previous work in the area showing two distinctive patterns of gastritis in patients receiving NSAIDs, chronic and reactive gastritis. Chronic gastritis in patients receiving NSAIDs has a strong association with *H pylori* but most studies show a similar¹⁷⁻²² or slightly reduced²³⁻²⁶ carriage rate of the organism compared with that of chronic gastritis not associated with NSAIDs, suggesting that the lesion is incidental rather than caused by NSAIDs. Changes of reactive gastritis are in most instances incompatible with *H pylori* infection^{17 27 28} and vice versa, but it is not presently possible to say whether chemical gastritis is associated with changes that are unfavourable to *H pylori* colonisation or whether the histopathological changes associated with *H pylori* associated chronic gastritis overshadow the subtle changes of reactive gastritis.¹⁷

When fully developed, reactive gastritis is easily identified and characterised by considerable foveolar hyperplasia associated with a comparative paucity of inflammation. In a few it may be difficult to distinguish between

mild reactive changes and apparently normal mucosa.¹⁷ Reactive gastritis is not pathognomonic for NSAID induced damage as it is also commonly seen in bile acid induced damage in the intact and postoperative stomach.^{28 29} The mechanism of damage is uncertain. Because of the different chemical nature of NSAIDs and bile acids, reactive gastritis probably does not represent specific biochemical abnormality. Rather the histological changes may represent a tissue reaction in response to an effect on cell membranes, as both the drugs and bile have detergent properties.^{30 31}

Our studies show that longterm coadministration of misoprostol with NSAIDs specifically reduces the prevalence of reactive gastritis but has no effect on the *H pylori* associated chronic gastritis. That misoprostol either prevents the occurrence of reactive gastritis or reverses it lends further credence to the idea that such a pattern is a specific entity of which at least one of the causes is chemical induction by NSAIDs.²⁹ That misoprostol, in diminishing the adverse mucosal effects of NSAIDs, does not influence the prevalence of *H pylori* gastritis in this cohort of patients also suggests that *H pylori* gastritis in these patients is incidental.^{19 32} Furthermore, misoprostol coadministration increases the total percentage of normal biopsy specimens at the expense of those showing reactive gastritis, the last pattern being hostile to *H pylori* colonisation. It might therefore have been expected that the *Helicobacter* colonisation rate and concomitant chronic gastritis would have increased in the misoprostol treatment group. That this was not seen supports the broad epidemiological concept that reinfection by *H pylori* is a rare event in the adult population. The clinical implications of the study are more uncertain. An intriguing possibility is that the reduced prevalence of reactive gastritis in patients receiving misoprostol may somehow underlie its effect to reduce the incidence of ulcers when given concomitantly with NSAIDs.^{15 33 34} Patients with NSAID associated ulcers, however, have an equal prevalence of reactive and *H pylori* associated chronic gastritis, 54% and 48%, respectively,²⁴ and we have shown that misoprostol only reduces the prevalence of the first. Nevertheless by analogy with classic peptic ulcer disease, which is almost invariably associated with the presence of *H pylori* related

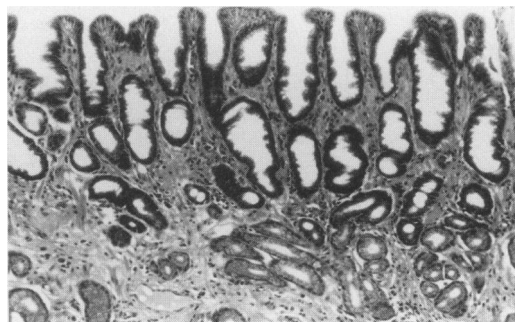


Figure 2: Typical reactive (chemical, type C) gastritis with prominent foveolar hyperplasia, some loss of antral glands, muscle like fibres in the mucosa and, most important, a paucity of inflammatory cells (haematoxylin and eosin, original magnification $\times 160$).

chronic gastritis,³⁵ gastric acid suppression with suitable drugs is sufficient to prevent ulcer recurrence when given longterm.³⁶⁻³⁷ This occurs despite the continuing presence of *H. pylori*. In this context it may be relevant that misoprostol has anti-secretory properties even at comparatively low doses.³⁸ Collectively this could explain the findings that prostaglandins prevent NSAID associated gastric and duodenal ulcer, while H₂ receptor antagonists only prevent the second,⁹⁻¹⁰ as misoprostol affects both pathogenic arms of the development of the ulcers in patients receiving NSAIDs and H₂ receptor antagonists only suppress gastric acidity. This is consistent with Graham's suggestion of separate aetiologies and pathogenesis of gastroduodenal ulcers in patients receiving NSAIDs³²⁻³⁹ namely a direct effect of NSAIDs and an independent effect on *H. pylori*.

In summary, we saw no worrying histopathological changes in gastric biopsy specimens of patients receiving longterm NSAIDs treatment and misoprostol. Indeed misoprostol specifically reduces the prevalence of reactive gastritis. Comparison of the findings from NSAID treated patients and those who were concomitantly taking misoprostol adds additional weight to the concept of dual gastric pathology in patients receiving NSAIDs: the reactive changes being a direct consequence of NSAIDs and largely reversible with prostaglandin treatment, and that of *H. pylori* positive chronic gastritis, which seems to be an incidental finding in patients receiving NSAIDs and not related to NSAID treatment.

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